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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02015229.4

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Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Demande no:

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Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Process for the production of N-monoalkyl Beta-amino alcohols

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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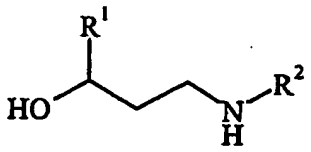
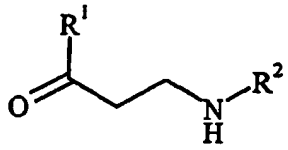
Description

The invention relates to an process for the preparation of *N*-monoalkyl β-amino alcohols of formula



(I)

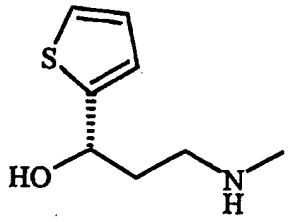
and their addition salts of proton acids via direct synthesis of *N*-monoalkyl β-keto amines of formula



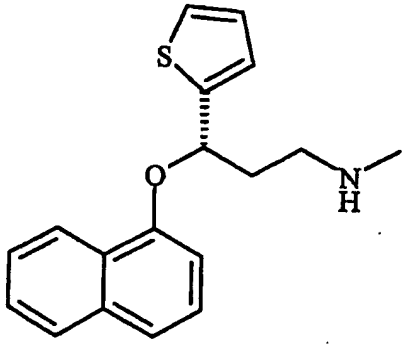
(II)

and their addition salts of proton acids.

N-monoalkyl β-amino alcohols are useful as key intermediates and building blocks (e.g. LY293628) for the preparation of pharmaceutically active compounds like Duloxetine, which acts as neuro-active compound [H. Liu et al.; Chirality, 12 (2000), 26-29.].



LY293628

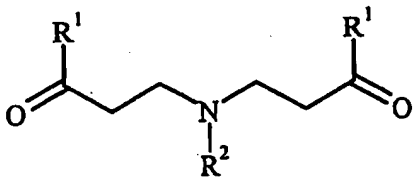


Duloxetine

In the following the terms "amine" or "amines" include the corresponding addition salts of proton acids.

Direct preparation of *N*-monoalkyl β-keto amines of formula I establishes an alternative and economically advantageous source for industrial production of *N*-monoalkyl β-amino alcohols of formula II.

Compounds of formula II were first synthesized in 1922 by C. Mannich who described a reaction of ketones with formaldehyde and primary or secondary alkylamines in the presence of hydrochloric acid [C. Mannich; G. Heilner; 55 (1922), 356-365.]. In reactions with primary alkylamines formation of hydrochlorides of tertiary β-keto amines of formula



(III)

overrules the formation of hydrochlorides of secondary β-keto amines of formula II. These findings were supported by Blicke et al. [F.F. Blicke; J.H. Burckhalter; J. Am. Chem. Soc., 64 (1942), 451-454.] and Becker et al. [H.G.O. Becker; W. Ecknig; E. Fanghänel; S. Rommel; Wissenschaftl. Zeitschr., 11 (1969) 38-41].

According to Mannich steam destillation of tertiary β-keto amines of formula III results in secondary β-keto amines in fairly satisfactory yields accompanied by vinyl compounds and other byproducts.

In spite of the loss of more than 50 % of the starting compounds and due to lack of alternative processes this procedure is still used as a main way for the preparation of secondary β-keto amines.

Another drawback in all current preparation methods is the need of isolation of the desired intermediate compounds of formula (II) from the majority of compounds of formula (III).

EP-A 457 559, EP-A 650 965 disclose the preparation of *N,N*-dimethyl β-amino alcohols via Mannich-type reactions of methyl ketones with paraformaldehyde and dimethylamine to get *N,N*-dimethyl β-amino ketones followed by reduction of the carbonyl group. After reaction of the hydroxyl group affording alkyl or aryl ether derivatives one methyl radical is then removed.
In case of *N,N*-dimethyl β-keto amines removing of one methyl radical requires delicate and expensive further reactions.

Only Becker et al. discloses some few examples with yields of about 60% of *N*-monomethyl β-keto amines using *N*-methylammonium oxalates as nitrogen source. Nevertheless, the process disclosed by Becker et al. is not advantageous because it depends strictly on the use of amino oxalates. Oxalates of primary amines are not commercially available, in contrast to the free amines or their hydrochloride. Furthermore, methylamine hydrochloride is easily available, cheap and, since it is a solid compound, easy to handle.

Using oxalates is also disadvantageous because it requires additional reduction equivalents in the next step, reducing the ketone intermediates to the title compounds.

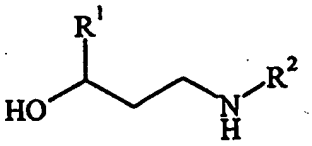
The problem to be solved was to provide a process for the synthesis of *N*-monoalkyl β-amino alcohols via direct preparation of *N*-monoalkyl β-amino ketones in high yields. Attaining independence of the commercial availability of the amine salts used in the reaction was another main target, as well as the possibility to produce any salt of the desired products. Furthermore, the proposed process should provide high yields independently of steric aspects of the used amino or carbonyl compounds.

The problems mentioned above could be solved according to claim 1.

Starting with commercially available methyl ketones and addition salts of primary amines, which were reacted in the presence of formaldehyde, a proton acid and a solvent at a pressure above 1.5 bar *N*-monoalkyl β-amino ketones which could be

directly reduced to the desired *N*-monoalkyl β-amino alcohols were obtained in high yields.

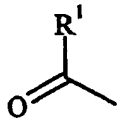
The present invention discloses a process for the preparation of a compound of formula



(I)

wherein R^1 and R^2 independently represent alkyl, cycloalkyl, aryl or aralkyl, each being optionally further substituted with alkyl, alkoxy and/or halogen, which process comprises

a) reacting a methyl ketone of formula



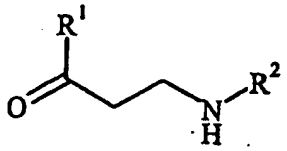
(IV)

wherein R^1 is as defined above, with

(i) a compound of formula

$H_2N—R^2$ (V)

wherein R^2 is as defined above and/or an addition salt of a proton acid thereof, (ii) formaldehyde or source of formaldehyde selected from the group consisting of formaldehyde in aqueous solution, 1,3,5-trioxane, paraformaldehyde and mixtures thereof; (iii) a solvent selected from the group consisting of water, aliphatic alcohols, cycloaliphatic alcohols and mixtures thereof, in the presence of (iv) a proton acid, to afford a compound of formula



(II)

and/or an addition salt of a proton acid, and

b) reducing the carbonyl group of said β-amino ketone to afford a compound of formula I, and/or an addition salt of a proton acid,

wherein the first step is carried out at a pressure above 1.5 bar.

In a preferred embodiment R^1 and R^2 independently represent linear or branched C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl, naphthyl, furanyl, benzofuranyl, thienyl, benzo[b]thienyl, or alkyl, wherein the alkyl moiety of the aralkyl residue is linear C_{1-4} alkyl, and the aryl moiety is selected from the group consisting of phenyl, naphthyl, furanyl, benzofuranyl, thienyl and benzo[b]thienyl, each aryl or aralkyl being optionally substiuted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cycloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5.

It is particularly preferred that R^1 represents furyl or thienyl.

It is also particularly preferred that R^2 represents linear or branched C_{1-8} alkyl. More particularly preferred R^2 represents methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl or *tert*-butyl.

Preferably, the compound of formula V is used as a free amine and/or an addition salt of a proton acid thereof. Particularly preferred are free amines, formates, acetates, oxalates, hydrochlorides, hydrobromides or mixtures thereof. More particularly preferred are free amines and/or hydrochlorides thereof.

In a preferred embodiment the compound of formula V is present in an amount at least equimolar to that of the compound of formula IV. Particularly prefererably the molar ratio the amount of the compound of formula V to the amount of the compound of formula IV is between 1 to 2.

The proton acid can be any carboxylic or inorganic acid, the acid being preferably selected from the group consisting of formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, benzoic acid, HF, HCl, HBr, HI, H_2SO_4, H_3PO_4. In a preferred embodiment the proton acid can be an acidic salt of a polybasic organic or inorganic acids like monoalkyli metal malonate, alkali metal hydrogensulfate, alkali metal hydrogenphosphate and alkali metal hydrogencarbonate.
More preferably the proton acid is selected from the group consisting of formic acid, acetic acid, propionic acid, oxalic acid, HCl and HBr, more preferably it is selected from the group consisting of formic acid, acetic acid, HCl and HBr.

In a preferred embodiment the solvent contains water, an aliphatic or cycloaliphatic alcohol or a mixture thereof.

Particularly preferred alcohols are linear or branched aliphatic C_{1-12} alcohols, cycloaliphatic C_{5-8} alcohols, di- and/or trimeric ethylene glycols or mono C_{1-4} alkyl or acetyl derivatives thereof, each of said alcohols containing 1 to 3 hydroxy groups.

Examples for said alcohols are methanol, ethanol, propanol, isopropanol, butanol, *sec*-butanol, *tert*-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 1-hexanol, 2-hexanol, cyclopentanol, cyclohexanol, 1,2-ethanediol, 1,2-propanediol, 1,2-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2,3-propanetriol, 1,2,6-hexanetriol, diethylene glycol, diethylene glycol mono-methyl ether, diethylene glycol mono-ethyl ether, diethylene glycol mono-butyl ether, diethylene glycol monoacetate, triethylene glycol, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-butyl ether, triethylene glycol monoacetate.

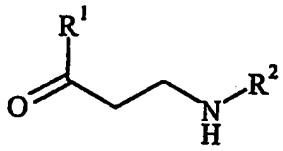
Preferably said alcohol is ethanol, propanol, isopropanol, butanol, *sec*-butanol, *tert*-butanol, diethylene glycol or triethylene glycol.

In a preferred embodiment the pressure during the reaction is above 1.5 bar, more preferably in the range of 1.5 to 10 bar and particularly preferred in the range of 1.5 to 5 bar.

In contrast to Becker et al. the inventive process generally leads to *N*-monoalkyl β-keto amines and all possible addition salts of proton acids. The products obtained by the inventive process can be reduced or subsequently reacted without further conversion into other salts.

None of the known processes for the production of *N*-monoalkyl β-amino alcohols of formula I includes, intends or reaches intermediate products comparable to *N*-monoalkyl β-keto amines of formula II of the present invention. Although still many efforts were made to find new preparation processes, the process of the present invention for direct synthesis of *N*-monoalkyl β-keto amines and subsequent reduction to *N*-alkyl β-amino alcohols is not yet disclosed.

The present invention also provides a compound of formula



(II)

and addition salts of a proton acid thereof,

wherein R^1 represents furyl, benzofuranyl, isobenzofuranyl, thienyl, benzo[b]thienyl, each being optionally substituted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cyloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5; and

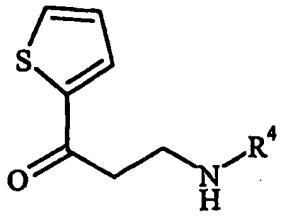
wherein R^2 is selected from the group consisting of

linear or branched C_{1-8} alkyl, C_{3-8} cyloalkyl, phenyl, naphthyl, furanyl, benzofuranyl, thienyl, benzo[b]thienyl, and aralkyl, wherein the alkyl moiety of the aralkyl residue is linear C_{1-4} alkyl, and the aryl moiety is selected from the group consisting of phenyl, furanyl, benzofuranyl, thienyl and benzo[b]thienyl,

each aryl or aralkyl being optionally substituted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cyloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5

with the exception of the compound wherein R^1 is thienyl and R^2 is benzyl.

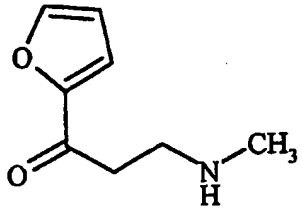
The present invention also provides a compound of formula



(VI)

and addition salts of a proton acid thereof, wherein R^4 represents methyl, ethyl, *sec*-butyl and *tert*-butyl.

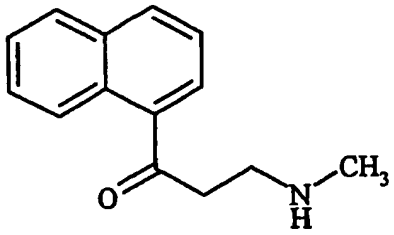
The present invention also provides a compound of formula



(VII)

and addition salts of a proton acid thereof.

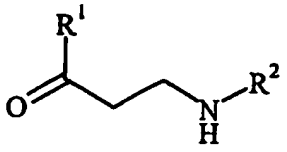
The present invention also provides a compound of formula



(VIII)

and addition salts of a proton acid thereof.

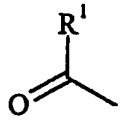
The present invention also provides a process for the preparation of a compound of formula



(II)

wherein R^1 and R^2 independently represent alkyl, cycloalkyl, aryl or aralkyl, each being optionally further substituted with alkyl, alkoxy and/or halogen,

which process comprises reacting a methyl ketone of formula



(IV)

wherein R^1 is as defined above, and

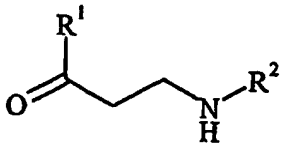
(i) a compound of formula

$H_2N—R^2$ (V)

wherein R^2 is as defined above, and/or an addition salt of a proton acid thereof,

(ii) formaldehyde or a source of formaldehyde selected from the group consisting of formaldehyde in aqueous solution, 1,3,5-trioxane, paraformaldehyde and mixtures thereof; and (iii) a solvent selected from the group consisting of water, aliphatic alcohols, cycloaliphatic alcohols and mixtures thereof, in the presence of (iv) a proton acid

to afford a compound of formula



(II)

wherein R^1 and R^2 are as defined above and/or an addition salt of a proton acid thereof,

and wherein the reaction is carried out at a pressure above 1.5 bar.

In a preferred embodiment R^1 and R^2 independently represent
linear or branched C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl, naphthyl, furanyl, benzofuranyl, thienyl, benzo[b]thienyl, and aralkyl, wherein the alkyl moiety of the aralkyl residue is linear C_{1-4} alkyl, and the aryl moiety is selected from the group consisting of phenyl, naphthyl, furanyl, benzofuranyl, thienyl and benzo[b]thienyl,
each aryl or aralkyl being optionally substituted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cycloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5.

It is particularly preferred that R^1 represents furyl or thienyl.
It is also particularly preferred that R^2 represents linear or branched C_{1-8} alkyl. More particularly preferably R^2 represents methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl or *tert*-butyl.

Preferably, the compound of formula V can be used as a free amine and/or an addition salt of a proton acid thereof. Particularly preferred are free amines, formates, acetates, oxalates, hydrochlorides, hydrobromides or mixtures thereof. More particularly preferred are free amines and/or hydrochlorides thereof.

In one preferred embodiment the compound of formula V is present in an amount at least equimolar to that of the compound of formula IV. Particularly prefererably the molar ratio the amount of the compound of formula V to the amount of the compound of formula IV is between 1 to 2.

The proton acid can be any carboxylic or inorganic acid, the acid being preferably selected from the group consisting of formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, benzoic acid, HF, HCl, HBr, HI, H_2SO_4, H_3PO_4. In a preferred embodiment the proton acid can be an acidic salt of a polybasic organic or inorganic acids like monoalkyli metal malonate, alkali metal hydrogensulfate, alkali metal hydrogenphosphate and alkali metal hydrogencarbonate. More preferably the proton acid is selected from the group consisting of formic acid, acetic acid, propionic acid, oxalic acid, HCl and HBr, more preferably it is selected from the group consisting of

formic acid, acetic acid, HCl and HBr.

In a preferred embodiment the solvent contains water, an aliphatic or cycloaliphatic alcohol or a mixture thereof.

Particularly preferred alcohols are linear or branched aliphatic C_{1-12} alcohols, cycloaliphatic C_{5-8} alcohols, di- and/or trimeric ethylene glycols or mono C_{1-4} alkyl or acetyl derivatives thereof, each of said alcohols containing 1 to 3 hydroxy groups.

Examples for said alcohols are methanol, ethanol, propanol, isopropanol, butanol, *sec*-butanol, *tert*-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 1-hexanol, 2-hexanol, cyclopentanol, cyclohexanol, 1,2-ethanediol, 1,2-propanediol, 1,2-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2,3-propanetriol, 1,2,6-hexanetriol, diethylene glycol, diethylene glycol mono-methyl ether, diethylene glycol mono-ethyl ether, diethylene glycol mono-butyl ether, diethylene glycol monoacetate, triethylene glycol, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-butyl ether, triethylene glycol monoacetate.

Preferably said alcohol is ethanol, propanol, isopropanol, butanol, *sec*-butanol, *tert*-butanol, diethylene glycol or triethylene glycol.

In a preferred embodiment the pressure during the reaction is above 1.5 bar, more preferably in the range of 1.5 to 10 bar and particularly preferred in the range of 1.5 to 5 bar.

Particularly preferred alcohols are linear or branched aliphatic C_{1-12} alcohols, cycloaliphatic C_{5-8} alcohols, di- and/or trimeric ethylene glycols or mono C_{1-4} alkyl or acetyl derivatives thereof, each of said alcohols containing 1 to 3 hydroxy groups.

Examples for said alcohols are methanol, ethanol, propanol, isopropanol, butanol, *sec*-butanol, *tert*-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 1-hexanol, 2-hexanol, cyclopentanol, cyclohexanol, 1,2-ethanediol, 1,2-propanediol, 1,2-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2,3-propanetriol, 1,2,6-hexanetriol, diethylene glycol, diethylene glycol mono-methyl ether, diethylene glycol mono-ethyl ether, diethylene

glycol mono-butyl ether, diethylene glycol monoacetate, triethylene glycol, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-butyl ether, triethylene glycol monoacetate.

Preferably said alcohol is ethanol, propanol, isopropanol, butanol, *sec*-butanol, *tert*-butanol, diethylene glycol or triethylene glycol.

In a preferred embodiment the pressure during the reaction is above 1.5 bar, more preferably in the range of 1.5 to 10 bar and particularly preferred in the range of 1.5 to 5 bar.

The present invention is illustrated by the following non-limiting examples.

General Procedure for Examples 1 to 8

A mixture of methyl ketone, primary alkyl amine and/or an addition salt thereof (1.1 to 1.5 equivalents (eq)), formaldehyde (1.4 to 1.5 eq), a solvent, optionally in the presence of a proton acid, is heated in an autoclave at a total pressure above 1.5 bar for 5 to 24 hours. Afterwards, the reaction solution is cooled to 20 °C. Optionally the reaction solvent can than be removed partly or in whole and a solvent like ethyl acetate or isopropanol can be added under vigorous stirring, if necessary to facilitate precipitation of the product. The suspension is cooled (0 to 20 °C°C) and after precipitation (0.5 to 10 hours) the product can be filtrated, optionally washed and dried affording a slightly yellow to white powder in yields between 50 to 75 %. The product can be recrystallized from isopropanol and/or ethyl acetate if necessary. If the stability of the free base is sufficient at ambient conditions, extracting with an organic solvent and an aqueous base affords the free base.

General Procedure for Comparative Examples 1 to 6

A mixture of methyl ketone, primary alkyl amine and/or an addition salt thereof (1 to 1.5 eq), formaldehyde (1.0 to 1.5 eq), optionally in the presence of a proton acid, is heated in refluxing solvent for 5 to 24 hours. Afterwards, the mixture is cooled to 20 °C. Optionally the reaction solvent can than be removed partly or in whole and a solvent like ethyl acetate or isopropanol can be added under vigorous stirring, if necessary to

facilitate precipitation of the product. The suspension is cooled (0 to 20 °C°C) and after precipitation (0.5 to 10 hours) the product can be filtrated, optionally washed and dried affording a slightly yellow to white powder in yields between 30 to 45 %. The product can be recrystallized from isopropanol and/or ethyl acetate if necessary.

Example 1:

3-(methylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = methyl)

2-acetylthiophene (25.5 g, 200 mmol); methylamine hydrochloride (14.9 g, 220 mmol, 1.1 eq); paraformaldehyde (8.2 g, 280 mmol, 1.4 eq); HCl conc. (1.0 g); ethanol (100 mL); 110 °C for 9 hours; ca. 2 to 2.5 bar; removing of ethanol (50 mL) *in vacuo*; addition of ethyl acetate (200 mL); ca. 71 % yield.

^{1}H-NMR δ (DMSO-d_6, 400 MHz): 9.16 (2 H, s, br), 8.07 (1 H, dd, J = 5.0, 1.0), 8.01 (1 H, dd, J = 3.8, 1.0), 7.29 (1 H, dd, J = 5.0, 3.8), 3.49 (2 H, t), 3.20 (2 H, t), 2.56 (3 H, s); ^{13}C-NMR δ (DMSO-d_6, 100 MHz): 189.9, 142.7, 135.4, 133.8, 128.8, 43.1, 34.6, 32.4.

Example 2:

3-(methylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = methyl)

2-acetylthiophene (24.9 g, 197 mmol); methylamine hydrochloride (14.8 g, 219 mmol, 1.1 eq); paraformaldehyde (8.3 g, 276 mmol, 1.4 eq); HCl conc. (1.1 g); isopropanol (100 mL); 110 °C for 8 hours; ca. 2 to 2.5 bar; addition of isopropanol (50 mL); ca. 65 % yield.

Comparative Example 1:

3-(methylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = methyl)

2-acetylthiophene (7.9 g, 300 mmol); methylamine hydrochloride (30.4 g, 450 mmol, 1.5 eq); paraformaldehyde (12.6 g, 420 mmol, 1.4 eq); HCl conc. (1.5 g); isopropanol (200 mL); heating under reflux (82 °C) for 8 hours; addition of ethyl acetate (200 mL); ca. 43 % yield.

Example 3:

3-(ethylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = ethyl)

2-acetylthiophene (6.3 g, 50 mmol); ethylamine hydrochloride (6.1 g, 75 mmol, 1.5 eq); paraformaldehyde (2.1 g, 75 mmol, 1.5 eq); HCl conc. (0.3 g); ethanol (35 mL); 110 °C for 9 hours; ca. 2 to 2.5 bar; removing of ethanol (25 mL) *in vacuo*; addition of ethyl acetate (50 mL); ca. 73 % yield.

^{1}H-NMR δ (DMSO-d_6, 400 MHz) : 9.3 (2 H, s, br), 8.08 (1 H, dd), 8.00 (1 H, dd), 7.28 (1 H, dd), 3.51 (2 H, t), 3.20 (2 H, t), 2.96 (2 H, q), 1.23 (3 H, t).

Comparative Example 2:

3-(ethylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = ethyl)

2-acetylthiophene (12.6 g, 100 mmol); ethylamine hydrochloride (12.2 g, 150 mmol, 1.5 eq); paraformaldehyde (4.1 g, 140 mmol, 1.4 eq); HCl conc. (0.5 g); ethanol (70 mL); heating under reflux (78 °C) for 6 hours; removing of ethanol (25 mL) *in vacuo*; addition of ethyl acetate (70 mL); ca. 31 % yield.

Example 4: 3-(isobutylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = isobutyl)

2-acetylthiophene (6.3 g, 50 mmol); isobutylamine hydrochloride (8.3 g, 75 mmol, 1.5 eq); paraformaldehyde (2.1 g, 75 mmol, 1.5 eq); HCl conc. (0.3 g); ethanol (35 mL); 110 °C for 9 hours; ca. 2 to 2.5 bar; removing of ethanol (35 mL) *in vacuo*; addition of ethyl acetate (50 mL); ca. 56 % yield.

^{1}H-NMR δ (DMSO-d_6, 400 MHz) : 9.0 (2 H, s, br), 8.08 (1 H, dd), 7.99 (1 H, dd), 7.29 (1 H, dd), 3.55 (2 H, t), 3.22 (2 H, t), 2.78 (2 H, d), 2.03 (1 H, m), 0.96 (6 H, d).

Comparative Example 3:

3-(isobutylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = isobutyl)

2-acetylthiophene (12.6 g, 100 mmol); isobutylamine hydrochloride (16.5 g, 150 mmol, 1.5 eq); paraformaldehyde (4.1 g, 140 mmol, 1.4 eq); HCl conc. (0.5 g); butanol (70 mL); heating under reflux (108 °C) for 7 hours; addition of ethyl acetate (100 mL);

ca. 40 % yield.

Example 5:

3-(*tert*-butylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = *tert*-butyl)

2-acetylthiophene (6.3 g, 50 mmol); *tert*-butylamine hydrochloride (8.3 g, 75 mmol, 1.5 eq); paraformaldehyde (2.1 g, 75 mmol, 1.5 eq); HCl conc. (0.3 g); butanol (35 mL); 117 °C for 9 hours; ca. 2 to 2.5 bar; addition of ethyl acetate (50 mL); ca. 52 % yield.

^{1}H-NMR δ (DMSO-d_6, 400 MHz) : 9.2 (2 H, s, br), 8.08 (1 H, dd), 7.98 (1 H, dd), 7.30 (1 H, dd), 3.54 (2 H, t), 3.19 (2 H, t), 1.34 (9 H, s).

Comparative Example 4:

3-(*tert*-butylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (II, R^1 = thiophen-2-yl, R^2 = *tert*-butyl)

2-acetylthiophene (12.6 g, 100 mmol); *tert*-butylamine hydrochloride (16.5 g, 150 mmol, 1.5 eq); paraformaldehyde (4.1 g, 140 mmol, 1.4 eq); HCl conc. (0.5 g); butanol (70 mL); heating under reflux (108 °C) for 18 hours; addition of ethyl acetate (100 mL); ca. 37 % yield.

Example 6:

3-(methylamino)-1-(furan-2-yl)propan-1-one hydrochloride (II, R^1 = furan-2-yl, R^2 = methyl)

2-acetylfuran (7.5 g, 68 mmol); methylamine hydrochloride (6.9 g, 102 mmol, 1.5 eq); paraformaldehyde (3.1 g, 102 mmol, 1.5 eq); HCl conc. (1.15 g); ethanol (35 mL); 110 °C for 8 hours; ca. 2 to 2.5 bar; removing of ethanol (30 mL) *in vacuo*; addition of ethyl acetate (50 mL); ca. 64 % yield.

^{1}H-NMR δ (DMSO-d_6, 400 MHz) : 9.0 (2 H, s, br), 8.05 (1 H, m), 7.53 (1 H, m), 6.77 (1 H, m), 3.34 (2 H, t), 3.2 (2 H, m), 2.57 (3 H, s, br).

Comparative Example 5:

3-(methylamino)-1-(furan-2-yl)propan-1-one hydrochloride (II, R^1 = furan-2-yl, R^2 = methyl)

2-acetylfuran (11.0 g, 100 mmol); methylamine hydrochloride (10.1 g, 150 mmol, 1.5 eq); paraformaldehyde (4.1 g, 140 mmol, 1.4 eq); HCl conc. (0.5 g); butanol (70 mL); heating under reflux (108 °C) for 7 hours; addition of ethyl acetate (100 mL); ca. 44 % yield.

Example 7:

3-(methylamino)-1-phenylpropan-1-one hydrochloride (II, R^1 = phenyl, R^2 = methyl)

2-acetophenone (21.0 g, 175 mmol); methylamine hydrochloride (17.5 g, 263 mmol, 1.5 eq); paraformaldehyde (7.9 g, 263 mmol, 1.5 eq); HCl conc. (1.1 g); ethanol (130 mL); 115 °C for 24 hours; ca. 2 to 2.5 bar; addition of ethyl acetate (170 mL); ca. 52 % yield.

^{1}H-NMR δ (DMSO-d_6, 400 MHz) : 9.2 (2 H, s, br), 8.0 (2 H, m), 7.7 (1 H, m), 7.6 (2 H, m), 3.55 (2 H, t), 3.21 (2 H, t), 2.59 (3 H, s).

Example 8:

3-(methylamino)-1-(2-naphthyl)propan-1-one hydrochloride (II, R^1 = 2-naphthyl, R^2 = methyl)

2-acetonaphtone (8.5 g, 50 mmol); methylamine hydrochloride (5.1 g, 75 mmol, 1.5 eq); paraformaldehyde (2.1 g, 75 mmol, 1.5 eq); HCl conc. (0.3 g); ethanol (35 mL); 117 °C for 14 hours; ca. 2 to 2.5 bar; removing of ethanol (35 mL) *in vacuo*; addition of ethyl acetate (50 mL); ca. 60 % yield.

^{1}H-NMR δ (DMSO-d_6, 400 MHz) : 9.3 (2 H, s, br), 8.74 (1 H, s), 8.17 (1 H, d), 8.0 (3 H, m), 7.7 (2 H, m), 3.70 (2 H, t), 3.28 (2 H, m), 2.60 (3 H, s).

Comparative Example 6:

3-(methylamino)-1-(2-naphthyl)propan-1-one hydrochloride (II, R^1 = 2-naphthyl, R^2 = methyl)

2-acetonaphtone (17.0 g, 100 mmol); methylamine hydrochloride (10.1 g, 150 mmol, 1.5 eq); paraformaldehyde (4.1 g, 140 mmol, 1.4 eq); HCl conc. (0.5 g); ethanol (70 mL); heating under reflux (78 °C) for 5 hours; removing of ethanol (30 mL) *in*

vacuo; addition of ethyl acetate (100 mL); ca. 42 % yield.

Example 9:

3-(methylamino)-1-(thiophen-2-yl)propan-1-ol (I, R^1 = thiophen-2-yl, R^2 = methyl)

To a mixture of 3-(methylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (10.3 g, 50 mmol) and ethanol (35 mL) at 4 °C sodium hydroxide (4.0 g of a 50 % aqueous solution) was added in about 5 minutes. Afterwards, neat sodium borhydride (0.95 g, 25 mmol, 1.0 equ.) was added in several portions in about 30 minutes. At the end of the addition, the suspension was stirred for 4 h at the same temperature, then acetone (10.0 mL) was added dropwise in 5 minutes and the mixture was stirred for 10 additional minutes. Water (20 mL) was then added. Afterwards, the mixture was concentrated about 5 times under vacuum and the residue was extracted with tert-butyl methyl ether (2 x 20 mL). The collected organic phases were finally concentrated under vacuum affording an orange oil which crystallised spontaneously after a few hours. Finally, an orange solid was obtained (7.2 g, 84 % yield). This compound can then be used without further purification.

^{1}H-NMR δ (DMSO-d6, 400 MHz) : 7.35 (1 H, dd, J = 4.8, 1.0), 6.94 (1 H, dd, J = 4.8, 3.6), 6.90 (1 H, dd, J = 3.6, 1.0), 4.90 (1 H, t), 3.7 (2 H, m), 2.56 (2 H, m), 2.25 (3 H, s), 1.79 (2 H, q); ^{13}C-NMR δ (DMSO-d6, 100 MHz) : 150.9, 126.3, 123.7, 122.3, 67.8, 48.5, 38.7, 36.0.

Example 10:

3-(isobutylamino)-1-(thiophen-2-yl)propan-1-ol (I, R^1 = thiophen-2-yl, R^2 = methyl)

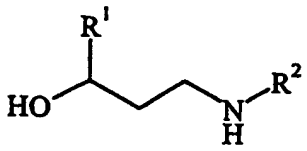
To a mixture of 3-(isobutylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (4.2 g, 19.4 mmol) and ethanol (10 mL) at 4 °C sodium hydroxide (1.6 g of a 50 % aqueous solution) was added in about 20 minutes. Afterwards, neat sodium borhydride (0.37 g, 9.7 mmol, 1.0 equ.) was added in several portions in about 30 minutes. At the end of the addition, the suspension was stirred for 4 h at the same temperature, then acetone (10.0 mL) was added dropwise in 20 minutes and the mixture was stirred for 10 additional minutes. Afterwards the precipitate was removed by filtration and the mixture was concentrated under vacuum affording an orange oil. The crude product was purified by column chromatography using a 40 : 10 : 1 (v : v : v) mixture of methylene chloride : methanol : ammonium hydroxide (25 % aqueous solution) affording 3.1 g

(76 % yield) of product.

^{1}H-NMR δ (DMSO-d6, 400 MHz) : 7.20 (1 H, dd, J = 4.8, 1.0), 6.98 (1 H, dd), 6.94 (1 H, dd, J = 4.8, 3.6), 5.20 (1 H, dd), 4.98 (2 H, br), 3.02 (1 H, m), 2.93 (1 H, m), 2.43 (2H, symm. m), 2.03 (1 H, m), 1.97 (1 H, m), 1.80 (1 H, sept), 0.95 (6 H, d); ^{13}C-NMR δ (DMSO-d6, 100 MHz) : 150.9, 126.3, 123.8, 122.5, 72.1, 57.8, 48.5, 37.4, 28.2, 20.8 (2C).

Claims

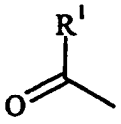
1. A process for the preparation of a compound of formula



(I)

wherein R^1 and R^2 independently represent alkyl, cycloalkyl, aryl or aralkyl, each aryl or aralkyl being optionally further substituted with alkyl, alkoxy and/or halogen, which process comprises

a) reacting a methyl ketone of formula



(IV)

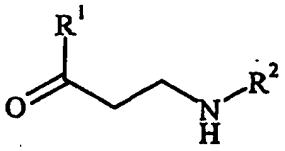
wherein R^1 is as defined above, and

(i) a compound of formula

$$H_2N—R^2 \qquad (V)$$

wherein R^2 is as defined above and/or an addition salt of a proton acid thereof, (ii) formaldehyde or a source of formaldehyde selected from the group consisting of formaldehyde in aqueous solution, 1,3,5-trioxane, paraformaldehyde and mixtures thereof; (iii) a solvent selected from the group consisting of water, aliphatic alcohols, cycloaliphatic alcohols and mixtures thereof, in the presence of (iv) a proton acid,

to afford a β-amino ketone of formula



(II)

or its addition salts of a proton acid, and

b) reducting the carbonyl group of said β-amino ketone to afford a compound of formula I, or its addition salts of a proton acid

wherein the first step is carried out at a pressure above 1.5 bar.

2. The process of claim 1 wherein R^1 is selected from the group consisting of linear or branched C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl, naphthyl, furanyl, benzofuranyl, thienyl, benzo[b]thienyl, and aralkyl, wherein the alkyl moiety of the aralkyl residue is linear C_{1-4} alkyl, and the aryl moiety is selected from the group consisting of phenyl, naphthyl, furanyl, benzofuranyl, thienyl and benzo[b]thienyl, each aryl or aralkyl being optionally substituted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cyloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5.

3. The process of claim 1 or 2 wherein R^2 is selected from the group consisting of linear or branched C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl, naphthyl, furanyl, benzofuranyl, thienyl, benzo[b]thienyl, and aralkyl, wherein the alkyl moiety of the aralkyl residue is linear C_{1-4} alkyl, and the aryl moiety is selected from the group consisting of phenyl, naphthyl, furanyl, benzofuranyl, thienyl and benzo[b]thienyl, each aryl or aralkyl being optionally substituted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cyloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5.

4. The process of any of claims 1 to 3, wherein the compound of formula V is present in an amount at least equimolar to that of the compound of formula IV.

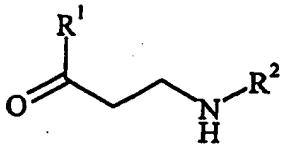
5. The process of any of claims 1 to 4, wherein the proton acid is a carboxylic or an inorganic acid, the acid being preferably selected from the group consisting of formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, benzoic acid, HF, HCl, HBr, HI, H_2SO_4, H_3PO_4, mono alkali metal malonate, alkali metal hydrogen-sulfate, alkali metal hydrogenphosphate and alkali metal hydrogencarbonate.

6. The process of any of claims 1 to 5, wherein aliphatic and cycloaliphatic alcohols are selected from the group selected of linear or branched aliphatic C_{1-12} alcohols, cycloaliphatic C_{5-8} alcohols, di- and/or triethylene glycols and mono C_{1-4} alkyl or acetyl derivatives thereof, each of said alcohols containing 1 to 3 hydroxy groups.

7. The process of claim 6, wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, *sec*-butanol, *tert*-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 1-hexanol, 2-hexanol, cyclopentanol, cyclohexanol, 1,2-ethanediol, 1,2-propanediol, 1,2-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2,3-propanetriol, 1,2,6-hexanetriol, diethylene glycol, diethylene glycol mono-methyl ether, diethylene glycol mono-ethyl ether, diethylene glycol mono-butyl ether, diethylene glycol monoacetate, triethylene glycol, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-butyl ether and triethylene glycol monoacetate.

8. The process of any of claims 1 to 7, wherein the pressure during the reaction is above 1.5 bar, more preferably in the range of 1.5 to 10 bar and more particularly preferred in the range of 1.5 to 5 bar.

9. A compound of formula

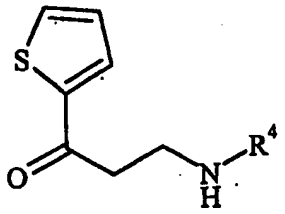


(II)

and its addition salts of proton acids, wherein R^1 represents
furyl, benzofuranyl, isobenzofuranyl, thienyl, benzo[b]thienyl,
each being optionally substituted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cyloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5; and
wherein R^2 is selected from the group consisting of
linear or branched C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl, naphthyl, furanyl, benzofuranyl, thienyl, benzo[b]thienyl, and aralkyl, wherein the alkyl moiety of the aralkyl residue is linear C_{1-4} alkyl, and the aryl moiety is selected from the group

consisting of phenyl, naphthyl, furanyl, benzofuranyl, thienyl and benzo[b]thienyl, each aryl or aralkyl being optionally substituted with halogen, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy, C_{3-6} cyloalkyl, CF_3, C_2F_5, OCF_3 or OC_2F_5 with the exception of the compound wherein R^1 represents thienyl and R^2 represents benzyl.

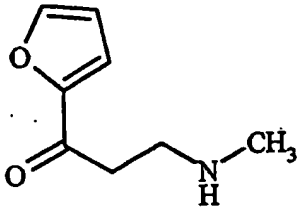
10. A compound of formula



(VI)

and its addition salts of proton acids, wherein R^4 represents methyl, ethyl, *sec*-butyl or *tert*-butyl.

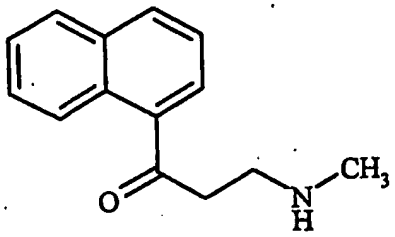
11. A compound of formula



(VII)

and its addition salts of proton acids.

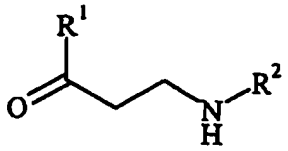
12. A compound of formula



(VIII)

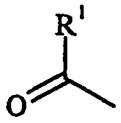
and its addition salts of proton acids.

13. A process for the preparation of a compound of formula



(II)

wherein R^1 and R^2 independently represent alkyl, cycloalkyl, aryl or aralkyl, each being optionally further substituted with alkyl, alkoxy and/or halogen, which process comprises reacting a methyl ketone of formula



(IV)

wherein R^1 is as defined above, and

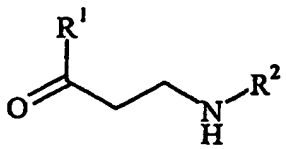
(i) a compound of formula

$H_2N—R^2$ (V)

wherein R^2 is as defined above and/or an addition salt of a proton acid thereof,

(ii) formaldehyde or a source of formaldehyde selected from the group consisting of formaldehyde in aqueous solution, 1,3,5-trioxane, paraformaldehyde and mixtures thereof; (iii) a solvent selected from the group consisting of water, aliphatic alcohols, cycloaliphatic alcohols and mixtures thereof, in the presence of (iv) a proton acid,

to afford a β-amino ketone of formula



(II)

and/or an addition salt of a proton acid thereof, wherein R^1 and R^2 are as defined above, and

wherein the reaction is carried out at a pressure above 1.5 bar.

14. The process of claim 13 wherein R^1 is as defined in claim 2.

15. The process of claim 13 or 14 wherein R^2 is as defined in claim 3.

16. The process of any of claims 13 to 15, wherein the compound of formula V is present in an amount at least equimolar to that of the compound of formula IV.

17. The process of any of claims 13 to 16, wherein the proton acid is a carboxylic or an inorganic acid, preferably the acid is selected from the group consisting of formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, benzoic acid, HF, HCl, HBr, HI, H_2SO_4, H_3PO_4, , mono alkali metal malonate, alkali metal hydrogen-sulfate, alkali metal hydrogenphosphate and alkali metal hydrogencarbonate.

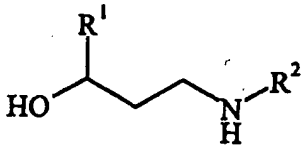
18. The process of any of claims 16 to 17, wherein aliphatic and cycloaliphatic alcohols are selected from the group consisting of linear or branched aliphatic C_{1-12} alcohols, cycloaliphatic C_{5-8} alcohols, di- triethylene glycols and mono C_{1-4} alkyl or acetyl derivatives thereof, each of said alcohols containing 1 to 3 hydroxy groups.

19. The process of claim 18, wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, isobutanol, *tert*-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 1-hexanol, 2-hexanol, cyclopentanol, cyclohexanol, 1,2-ethanediol, 1,2-propanediol, 1,2-butanediol, 2,3-butanediol, 1,4-butanediol, 1,2,3-propanetriol, 1,2,6-hexanetriol, diethylene glycol; methyl diethylene glycol, ethyl diethylene glycol, diethylene glycol mono-butyl ether, diethylene glycol monoacetate, triethylene glycol, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-butyl ether and triethylene glycol monoacetate.

20. The process of any of claims 13 to 19, wherein the pressure during the reaction is above 1.5 bar, more preferably in the range of 1.5 to 10 bar and more particularly preferred in the range of 1.5 to 5 bar.

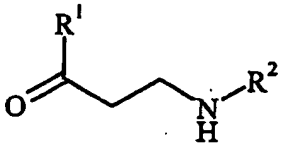
Summary

The invention provides a process for the synthesis of *N*-monoalkyl β-amino alcohols of formula



(I)

wherein and R^1 and R^2 independently represent alkyl, cycloalkyl, aryl or aralkyl, each being optionally further substituted with alkyl, alkoxy and/or halogen
via direct preparation of *N*-monoalkyl β-amino ketones of formula



(II)

wherein and R^1 and R^2 are as defined above.
The proposed process provides high yields independently of steric aspects of the used amino or carbonyl compounds.

Basel, July 5, 2002
Dr. B. Gallasch